A Clinical Trial of Efficacy of Antiproteolytic Therapy: Can It Be Done?[1,2]

BENJAMIN BURROWS

In recognition of the growing interest in the development of antiproteolytic therapies for emphysema, the Lung Division of the National Heart and Blood Institute convened, in October 1978, a Working Group for Evaluation of Elastase Inhibitor Therapy in Pulmonary Emphysema. (The membership of this Working Group is indicated at the end of this paper.) Several conclusions were reached and recommendations made at this meeting. Most had to do with the development of improved antiproteolytic materials and studies of their pharmacology. The development of chemical markers of lung destruction in emphysema was also considered a high priority.

In regard to possible clinical trials of therapies that looked promising, it was recommended that any initial trial should be carried out on alpha-1-antitrypsin deficient PiZ subjects, because the emphysema of such subjects is clearly related to an antiprotease deficiency and should be more likely prevented or ameliorated by replacement therapy than in patients without demonstrable antielastase deficiency. However, it was recognized that little was known about the natural history of PiZ disease and that if this was as variable as that of "ordinary" chronic obstructive pulmonary disease (COPD), very large numbers of subjects would need to be followed for a prolonged period to demonstrate significant beneficial effects on progression of disease or on mortality. It was suggested that much might be learned by examining data already available in the United States and other countries regarding mortality and rates of functional decline in PiZ subjects. It was recommended that a workshop be convened to collect, discuss, and interpret the compiled information.

A Workshop on the Natural History of the PiZ Subjects was subsequently convened in March 1980 under the auspices of the Lung Division. Participants were invited to bring with them as many examples of PiZ disease as possible. The purpose of this report is to summarize the discussions at that workshop and to explain some of its conclusions.

Ideally, one might wish to carry out a trial of the ability of antiprotease administration to prevent the emergence of disease in asymptomatic PiZ subjects. Unfortunately, the proportion of PiZ subjects who develop emphysema is unknown, and the age of onset of frank disease appears to be quite variable. Thus there would be no way to determine sample sizes needed to determine the efficacy of therapy; very large numbers of subjects would probably be required. Furthermore, recruitment of large numbers of asymptomatic PiZ subjects would present a serious logistic problem. For this reason, it was felt that primary prevention efforts to demonstrate efficacy of therapy would be impractical, at least as a first step.

The possibility of using late stage PiZ emphysema cases was next considered, using mortality as an outcome. The fact that mortality is a clearly identifiable end point is a clear advantage in such a study. Also, by identifying patients with an expected high mortality, significant differences might be noted within a few years, as was the case in the Nocturnal Oxygen Therapy Trial (1). In that study, significant differences in mortality were noted in a sample of a few hundred COPD patients followed for less than three years.

Despite these potential advantages, the group believed that there were overriding disadvantages in studying preterminal illness. First, the late stages of the disease may be "self-perpetuating" and too late for antiprotease to be effective. Also, the relationship of mortality to the stage of the disease is unknown in untreated PiZ emphysema. If it resembles ordinary COPD, initial functional levels, age, and evidences of cardiac disease become critical variables (2) that would need to be controlled. Furthermore, a high rate of intercurrent diseases might greatly influence results, especially in older subjects.

The conclusion of the group was that the best type of clinical trial would involve PiZ subjects already showing definite but relatively mild airways obstruction. This would provide an opportunity to arrest progression of the emphysematous process at a relatively early stage when rates of progression might be discernibly altered. Even such a study is fraught with problems, however.

Because mortality rates would be expected to be relatively low in these patients, the rate of decline in function would be the only practical end point of the study. Rates of decline are relatively slow and show wide variability in subjects with "ordinary" COPD. Whether the rates of decline in ventilatory function are as low and as variable in PiZ emphysema is unknown. If they are similar to those in ordinary COPD, enormous numbers of experimental and control subjects might be needed to show significant differences between treated and untreated groups.

The magnitude of the variability in rates of decline is exemplified in table 1, representing data from a study of 200 COPD patients enrolled in an emphysema study in Chicago more than 20 years ago (3). The variability in rates of functional loss is very high when there are only a few years of follow-up, but variability decreases with time of study. Obtaining more frequent observations tends to reduce the standard deviations of calculated regression slopes, but only to a limited extent, because the inherent fluctuations in FEV_1 measurements may actually exceed the calculated rates of decline for the first few years of follow-up. Because the sample size needed to demonstrate significant differences between experimental and control groups depends not only on the reduction in mean decline in the experimental group but on the standard deviations around this mean decline, enormous sample sizes would be required with less than three years of follow-up.

TABLE 1

RATES OF DECLINES IN FEV, AND THEIR STANDARD DEVIATIONS (S.D.) IN UNSELECTED COPD SUBJECTS VERSUS LENGTH OF FOLLOW-UP (CHICAGO STUDY)

Duration (yr)	Mean Decline (ml)	S.D. (ml)
1	−83	218
2	−69	153
3	−62	97
4	−57	83
5	−56	85
6	−58	84

Based on the assumption that PiZ emphysema would behave like "ordinary" COPD, Dr. Margaret Wu, mathematical statistician for the Heart, Lung, and Blood Institute, calculated sample sizes (combined equal-sized experimental and control groups) needed to show significant differences ($p < 0.05$) between the rates of decline of treated and untreated subjects. As seen in table 2, these depend both on the proposed duration of follow-up and on the anticipated magnitude of the effect. It was believed that it would be unrealistic to expect more than a 50% rate of decline because this would give the experimental group a rate of fall close to that of the normal population. As can be seen from the table, 300 to 500 subjects would be required for a therapeutic trial with a minimum follow-up of three years. Many of us believe that enrollment of

[1] From the Division of Respiratory Sciences, University of Arizona College of Medicine, Tucson, Arizona.

[2] Supported in part by SCOR Grant No. HL-14136 from the National Heart, Lung, and Blood Institute.

TABLE 2

MINIMAL SAMPLE SIZES OF PiZ DISEASE TO SHOW A SIGNIFICANT DIFFERENCE BETWEEN TREATED AND CONTROLS IF TREATED SHOWED A 40% OR 50% REDUCTION IN DECLINE IN FEV,*

Years follow	Number if 50%	Number if 40%
3	336	524
5	316	494
7	290	454

* Assuming as much variance as in unselected COPD.

this number of PiZ subjects might be difficult indeed.

All of this presumes that PiZ disease is as variable as ordinary emphysema. If it were more stereotypic in its behavior, the numbers might be greatly reduced. To see how stereotypic PiZ disease appeared to be, participants in the Workshop were asked to examine retrospectively their data on the characteristics and courses of their PiZ patients. In this way, a large number of anecdotes were assembled and discussed at the PiZ workshop mentioned above. There was almost universal agreement that a minority of PiZ patients had the typical uncomplicated emphysema so often described as characteristic of PiZ disease. Also, there appeared to be wide variability in the course and prognosis of these patients, similar to that seen in "ordinary COPD." However, it was felt that more complete data were needed before final conclusions could be reached. Various physicians around the country and in Sweden were asked to complete a standardized form describing the characteristics and courses of their PiZ patients and submit these to Dr. Margaret Wu in Bethesda. These data have been checked and are being analyzed. Hopefully, they will indicate a lesser variability in rate of decline than was suggested by a less formal look at preliminary data.

At the time of this symposium, it is difficult to say whether a clinical trial of antiproteases in PiZ disease is feasible or not. This will depend on some of the statistical considerations already discussed. It will also depend, however, on the nature, expense, and difficulty of applying any proposed antiprotease program. It is clear, however, that any trial of antiprotease therapy will require a large multi-center effort with screening of all patients with persistent airflow limitation for Pi phenotype if adequate numbers of patients are to be assembled for a meaningful clinical trial.

Membership of the Working Group for Evaluation of Elastase Inhibitor Therapy in Pulmonary Emphysema: Allen B. Cohen, M.D., Ph.D., Chairman; Benjamin Burrows, M.D.; Ronald Crystal, M.D.; Graham Jamieson, Ph.D.; Aaron Janoff, Ph.D.; Alan Johnson, M.D.; Philip Kimbel, M.D.; James C. Powers, Ph.D.; Richard C. Talamo, M.D.; Gerard M. Turino, M.D.; Margaret Wu, Ph.D.

Participants in the "Workshop on the Natural History of The PiZ Subject" meeting in March 1980 included: Robert C. Allen, Ph.D.; Leo F. Black, M.D.; Sonia Buist, M.D.; Benjamin Burrows, M.D.; Bernice H. Cohen, Ph.D.; Allen B. Cohen, M.D., Ph.D.; Ronald Crystal, M.D.; Robert J. Fallat, M.D.; Morton Galdston, M.D.; Philip Kimbel, M.D.; Christer Larsson, M.D.; Stewart A. Lonky, M.D.; Charles Mittman, M.D.; John A. Pierce, M.D.; Gerard M. Turino, M.D.; and Margaret Wu, Ph.D.

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2. Traver GA, Cline MG, Burrows B. Predictors of mortality in chronic obstructive pulmonary disease. Am Rev Respir Dis 1979; 119: 895–902.

3. Burrows B. An overview of obstructive lung disease. Med Clin North Am 1981; 65:455–71.

The Natural History of Air-flow Obstruction in PiZ Emphysema[1–4]

REPORT OF AN NHLBI WORKSHOP

Prepared by A. Sonia Buist, Benjamin Burrows, Sten Eriksson, Charles Mittman, and Margaret Wu[4]

Introduction

The association between severe alpha-1-antitrypsin (AAT) deficiency and pulmonary emphysema was first described by Eriksson in the early 1960s (1, 2). These initial reports created considerable interest and provided the first real evidence that protease inhibitor factors in serum play an important part in maintaining the integrity of the lung parenchyma. A large body of evidence now supports the theory that emphysematous destruction results from an imbalance between proteolysis and antiproteolysis within the lung. However, little is known about the natural history of patients with emphysema resulting from severe AAT deficiency.

The data reported here were gathered by a group of investigators who participated in a workshop convened by the Division of Lung Diseases, National Heart, Lung and Blood Institute (NHLBI). The primary purpose of the workshop was to determine the feasibility of a clinical trial of antiproteolytic replacement therapy in PiZ subjects, should such therapy become available in the near future. In order to address this question, it was necessary first to collect information on the natural history of airflow obstruction in PiZ disease.

Retrospective data on PiZ individuals, which had been collected at many institutions in the United States, were reviewed. Also, comparable data were obtained for PiZ subjects seen in Sweden. We examined the natural history of the airflow obstruction, as reflected in the rate of decline of the 1-s forced expiratory volume (FEV_1). There was good agreement between results in American and Swedish subjects, giving us some confidence that the rates of decline of lung function observed may be reasonably representative of the rates of decline of function that occur in the subset of PiZ individuals who develop frank airflow limitation.

Methods

Information was provided by workshop members on 298 individuals living or having lived in the United States and who were known to have an AAT deficiency state. Sources of data included: (*1*) patients with lung disease, (*2*) relatives of such patients,

[1] A report of a workshop on the natural history of PiZ emphysema, sponsored by the Lung Division of the National Heart, Lung and Blood Institute, National Institutes of Health, Bethesda, Maryland. The workshop met on two occasions, March 19–20, 1980 and November 9, 1981.

[2] Workshop members: Robert C. Allen, Ph.D.; Leo F. Black, M.D.; A. Sonia Buist, M.D.; Benjamin Burrows, M.D.; Bernice H. Cohen, Ph.D.; Allen B. Cohen, M.D.; Sten Eriksson, M.D.; Robert J. Fallat, M.D.; Morton Galdston, M.D.; Stewart A. Lonky, M.D.; Harold A. Menkes, M.D.; Charles Mittman, M.D.; John A. Pierce, M.D.; Gerard M. Turino, M.D., and Margaret Wu, Ph.D.

[3] Requests for reprints should be addressed to A.S. Buist, M.D. Oregon Health Sciences University, Physiology Department L334, 3181 SW Sam Jackson Park Rd. Portland, OR 97201.

[4] All statistical analyses were carried out by Dr. M. Wu, mathematical statistician for the National Heart, Lung and Blood Institute.

TABLE 1

FINDINGS IN U.S. AND SWEDISH PiZ SUBJECTS WITH INITIAL FEV_1s BETWEEN 30- AND 65% OF PREDICTED

	U.S.	Swedish
Number of subjects	30	41
Mean age (SD), yr	45 (9)	47 (8)
Annual change in FEV_1, mean (SD), L	−0.111 (0.102)	−0.104 (0.094)
Initial FEV_1, % predicted, mean (SD), %	41.9 (10.7)	43.3 (9.6)
Months of follow-up,* mean (SD)	62 (36)	74 (47)
Percent males	50%	63%
Never smokers	3%	17%
Ex-smokers	80%	59%

* Number of months between first and last FEV_1 measurement.

(3) persons identified by blood bank screening, and (4) subjects identified in the course of population studies. For each subject, all known pulmonary function data were provided plus trypsin inhibitory capacity measurements, Pi phenotypes, age, height, and either date of death or daté last known alive. Initial and follow-up spirometric values were available on just over half of the subjects. After eliminating those who had not been shown to have a PiZ phenotype and those with duration between the reported initial and last FEV_1 measurements less than 12 months, 105 subjects from the United States remained for the study. Data collected on PiZ subjects seen in Sweden were provided by Dr. S. Eriksson. There were 41 Swedish patients meeting all the criteria mentioned above.

For the subjects included in the study, the number of FEV_1 measurements reported ranged from 2 to 12 (mean of 4.1) in the U.S. group and from 2 to 10 (mean of 3.8) from the Swedish group. The duration between the reported initial and last FEV_1s ranged from 13 to 149 months for the U.S. group and from 12 to 181 months for the Swedish group.

After preliminary analyses of the data on these subjects, it was decided that the most important group in terms of a possible therapeutic trial were those 30 U.S. subjects who, in addition to fulfilling the above criteria, were also less than 65 yr of age when first diagnosed and had an initial FEV_1 value between 30- and 65% of predicted (3). The reasons for concentrating on this group will be discussed below.

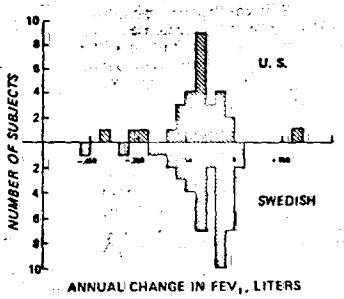

Fig. 1. Rate of change in 1-s forced expiratory volume (FEV_1) in liters/year for 30 U.S. subjects and 41 Swedish subjects with homozygous α_1-antitrypsin deficiency, PiZ phenotype. All subjects were under age 65 and had an FEV, between 30- and 65% of predicted (3).

Linear regression analysis was carried out separately for each individual to determine the annual rate of change in FEV_1.[4] From these analyses, group mean rates of decline were calculated and the standard deviations of these rates determined. Because our method of selecting subgroups for analysis could lead to some regression toward the mean, analyses were also carried out after deleting the initial FEV_1 levels, using only subjects with at least two subsequent follow-up studies. This analysis resulted in a 10% reduction in the mean rates of decline from those that included the initial data point. However, this method of analysis did reduce the number of subjects available for study. Consequently, because regression toward the mean did not appear to be affecting our results significantly, data reported here are based on analysis using all available FEV_1 values.

Results

Preliminary analyses showed that there was a small number of healthy young adults who were primarily detected in population surveys and who had normal or near normal FEV_1 values with very little, if any, decline in FEV_1 on follow-up. For example, there were 22 PiZ subjects in the U.S. group with an initial FEV_1 greater than 65% of predicted. This group had a mean age of 38 ± 12 years and a mean annual decline in FEV_1 of 42 ± 52 ml. It was also apparent that there was a high mortality but a quite low calculated rate of decline in subjects with FEV_1s below 30% of predicted. The 52 PiZ subjects in this group had a mean age of 46 ± 9 years and a mean annual decline of FEV_1 of 45 ± 8 ml.

Quite different rates of decline were noted in the 30 U.S. subjects under age 65 with FEV_1s in the 30–65% of predicted range. As seen in table 1, these subjects showed an annual decline in FEV_1 of 111 ± 102 ml. The majority of these patients came to the attention of investigators as patients. Data on 41 Swedish subjects showed very similar mean rates of decline and standard deviations. As also shown in table 1, the U.S. and Swedish subjects were very similar in regard to other characteristics, such as mean percent predicted FEV_1 on entry, sex distribution, and smoking habits. The distribution of rates of decline in the two series is shown in figure 1. Again, results are strikingly similar.

Discussion

Participants in the workshop fully recognize the limitations in data accumulated in the manner described. There is no assurance that the cases assembled are in any way representative of all PiZ subjects in the population. Indeed, as noted above, it is clear that not all persons with the PiZ phenotype develop overt disease. It is possible that their PiZ status was discovered only because of some unusual characteristic of their disease. In many instances, it was discovered because they developed overt disease. For this reason, direct comparisons with series of "ordinary COPD" subjects may not be totally valid. However, the rates of decline in FEV_1 observed in subjects with clinically significant but not end stage PiZ disease are nearly twice the average rates of decline reported in "ordinary COPD" (4).

In contrast, PiZ subjects who do not yet show a clinically significant degree of airways obstruction show much lower rates of decline. This may be explained in one of two ways. It is possible that the functional consequences of gradually progressive anatomic changes in the lungs of PiZ patients become manifest only after the disease is quite extensive. Functional changes may then progress relatively rapidly. This is compatible with observations of mild emphysematous changes in the lungs of PiZ patients dying of hepatitis at a young age (5). Alternatively, it is possible that not all PiZ subjects develop significant pulmonary disease and, unless one excludes such subjects, mean rates of functional decline may appear quite low.

At the other end of the spectrum, patients with very severe initial functional impairment cannot demonstrate high rates of decline because such declines would be incompatible with life. Thus, the low rates of decline in subjects with an initial FEV_1s below 30% of predicted are likely to represent a "survivor effect."

From the data presented, it would appear that PiZ subjects who develop clinically significant airflow limitation go through a phase of their disease in which there is a relatively high rate of functional decline. This is encouraging in regard to the feasibility of a trial of antiprotease therapy. It suggests that beneficial effects of such therapy could be demonstrated by showing a reduction in the rate of loss of function in subjects properly selected for such a clinical trial.

Acknowledgment

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